

Short Sleep Duration, Obstructive Sleep Apnea, Shiftwork, and the Risk of Adverse Cardiovascular Events in Patients After an Acute Coronary Syndrome

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Background—It is unknown whether short sleep duration, obstructive sleep apnea, and overnight shift work are associated with the risk of recurrent cardiovascular events in patients after an acute coronary syndrome.

Methods and Results—SOLID-TIMI 52 (The Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52 Trial) was a multinational, double-blind, placebo-controlled trial that enrolled 13 026 patients ≤ 30 days of acute coronary syndrome. At baseline, all patients were to complete the Berlin questionnaire to assess risk of obstructive sleep apnea and a sleep and shift work survey. Median follow-up was 2.5 years. The primary outcome was major coronary events (MCE; coronary heart disease death, myocardial infarction, or urgent revascularization). Cox models were adjusted for clinical predictors. Patients who reported < 6 hours sleep per night had a 29% higher risk of MCE (adjusted hazard ratio, 1.29; 95% confidence interval, 1.12–1.49; $P < 0.001$) compared with those with longer sleep. Patients who screened positive for obstructive sleep apnea had a 12% higher risk of MCE (1.12; 1.00–1.24; $P = 0.04$) than those who did not screen positive. Overnight shift work (≥ 3 night shifts/week for ≥ 1 year) was associated with a 15% higher risk of MCE (1.15; 1.03–1.29; $P = 0.01$). A step-wise increase in cardiovascular risk was observed for individuals with more than 1 sleep-related risk factor. Individuals with all 3 sleep-related risk factors had a 2-fold higher risk of MCE (2.01; 1.49–2.71; $P < 0.0001$).

Conclusions—Short sleep duration, obstructive sleep apnea, and overnight shift work are under-recognized as predictors of adverse outcomes after acute coronary syndrome. Increased efforts should be made to identify, treat, and educate patients about the importance of sleep for the potential prevention of cardiovascular events.

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Inadequate sleep, whether caused by reduced sleep duration or obstructive sleep apnea (OSA), and recurrent circadian disruption induced by night shift work adversely affect cardiovascular regulation^{1,2} and are associated with an increased risk of incident cardiovascular disease and death.^{3,4} Thirty percent of employed adults in the United States and

44% of night shift workers report sleeping, on average, 6 or fewer hours on work nights.⁵ Short sleep duration has been associated with increased risk for incident calcification of the coronary arteries,⁶ incident stroke,⁷ coronary heart disease,³ and death.^{8,9} In addition, prevalence of OSA has risen over the past 2 decades in the United States to an estimated 34% in

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Accompanying Tables S1, S2 and Figure S1 are available at <http://jaha.ahajournals.org/content/6/10/e006959/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- Past studies have not examined the clinical relevance of reduced sleep duration or sleep disruption in patients after an acute coronary syndrome.
- The current study demonstrates that short sleep duration, obstructive sleep apnea, and overnight shift work are independently associated with an increased risk of adverse cardiovascular outcomes through long-term follow-up.
- Moreover, the presence of ≥ 1 of sleep-related risk factors demonstrated an additive effect on cardiovascular risk.

What Are the Clinical Implications?

- Clinicians should be made aware of the observed association between short sleep duration and disrupted sleep and the risk of recurrent cardiovascular events after an acute coronary syndrome.
- Short sleep duration, obstructive sleep apnea, and a history of shift work should be routinely assessed in patients after an acute coronary syndrome.
- Increased efforts should be made to identify, treat and educate patients about the importance of sleep for the potential prevention of recurrent cardiovascular events after an acute coronary syndrome.

men and 17% in women.¹⁰ In turn, OSA is associated with incident ventricular arrhythmias,¹¹ incident cardiovascular risk,⁴ stroke,¹² and all-cause mortality.^{12,13} Misalignment between the timing of the sleep-wake cycle and endogenous circadian rhythms impairs cardiovascular regulation,² and night shift work is associated with hypertension^{14,15} and incident cardiovascular disease, including fatal and nonfatal myocardial infarctions (MIs).¹⁶ The adverse health consequences associated with short sleep duration, OSA, and shift work are similar, but it is not yet known whether they share common mechanisms of action.¹⁷

In particular, high-risk patients warrant further study. Patients are at increased risk of adverse outcomes after an acute coronary syndrome (ACS). However, it remains unknown whether sleep and circadian disruption may further increase cardiovascular risk in patients recovering from an ACS event. We therefore prospectively hypothesized that there would be an association between short sleep duration, OSA, overnight shift work, and cardiovascular events in a large population of ACS patients.

Methods

The design and results of the SOLID-TIMI 52 trial (Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52; ClinicalTrials.gov NCT 01000727) have been

previously reported.^{18,19} In brief, the SOLID-TIMI 52 trial was a double-blind, placebo-controlled phase 3 trial that enrolled 13 026 patients across 868 sites in 36 countries and randomized them to the investigational therapy, darapladib (an Lp-PLA₂ inhibitor), versus matching placebo. To be eligible for participation in the study, patients had to: (1) have been hospitalized within 30 days or fewer with an ACS and (2) have 1 additional cardiovascular risk factor (eg, age of at least 60 years, history of MI before the qualifying event). The trial was approved by the Partners Human Research Committee and all relevant institutional review boards worldwide. All participants provided written informed consent.

At the randomization visit (median 14 days post-ACS), each participant was to complete a short questionnaire about their sleep and shift work habits. To assess sleep duration, participants were asked, "On average, how much sleep do you get in 24 hours?" This question was very similar to the validated Behavioral Risk Factor Surveillance System question on sleep duration.²⁰ The validated Berlin Questionnaire was completed and standard scoring was used to designate individuals at increased risk of OSA regardless of whether or not they had a known history of OSA.²¹ The Berlin Questionnaire is scored as at risk for OSA if 2 of the 3 categories are positive (snoring and cessation of breathing, symptoms of excessive daytime sleepiness, and hypertension/body mass index [BMI] >30 kg/m²; see Figure S1 for questionnaire). In 8 small studies of cardiovascular or cerebrovascular disease patients, the specificity (26–76%) and sensitivity (40–93%) of the Berlin questionnaire varied depending on the apnea–hypopnea index thresholds and definition of hypopnea.²² Shift work history was also queried ("How many years have you worked at least THREE overnight shifts per week?").

Outcomes

The primary outcome for the trial was major coronary events (MCE; coronary heart disease death, MI, or urgent coronary revascularization for myocardial ischemia). Additional outcomes of interest for this analysis included major adverse cardiovascular events (MACE; cardiovascular death, MI, or stroke), MI (fatal or nonfatal), cardiovascular death, and all-cause mortality. All deaths, cardiac ischemic events, and cerebrovascular events were adjudicated by a clinical events committee who were blinded to treatment arm.

Statistics

Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. Prespecified dichotomous thresholds were applied to each sleep parameter to define short sleep duration (<6 hours), increased risk of OSA (high risk of OSA

Table. Baseline Characteristics

Baseline Characteristic	Obstructive Sleep Apnea (OSA)		Short Sleep		Overnight shift work		P Value
	No OSA	OSA	<6 Hours	≥6 Hours	No	Yes	
Age (y) (median, IQR)	65 (60, 71)	63 (57, 69)	64 (57, 71)	64 (59, 71)	64 (60, 71)	63 (57, 69)	<0.001
Age ≥60 y, n (%)	6293 (77.8)	3295 (68.1)	879 (70.1)	8691 (74.6)	7634 (76.1)	1942 (67.6)	<0.001
Female, n (%)	2072 (25.6)	1226 (25.4)	391 (31.2)	2898 (24.9)	2863 (28.5)	432 (15.0)	<0.001
Body mass index, kg/m ² (median, IQR)	26.35 (24.1, 28.7)	30.75 (27.2, 33.9)	27.99 (25.2, 32.2)	27.59 (24.8, 31.0)	27.36 (24.7, 30.8)	28.41 (25.6, 31.9)	<0.001
Race							
White, n (%)	6599 (81.6)	4274 (88.4)	1022 (81.5)	9833 (84.4)	8327 (83.0)	2531 (88.1)	<0.001
Black, n (%)	160 (2.0)	151 (3.1)	47 (3.7)	264 (2.3)	187 (1.9)	124 (4.3)	
Asian, n (%)	1186 (14.7)	337 (7.0)	147 (11.7)	1372 (11.8)	1359 (13.5)	159 (5.5)	
Other, n (%)	143 (1.8%)	74 (1.5)	38 (3.0)	179 (1.5)	158 (1.6)	59 (2.1)	
Region							
North America, n (%)	1399 (17.3)	1403 (29.0)	315 (25.1)	2484 (21.3)	1974 (19.7)	822 (28.6)	
South America, n (%)	606 (7.5)	347 (7.2)	114 (9.1)	838 (7.2)	642 (6.4)	311 (10.8)	
Western Europe, n (%)	2270 (28.1)	1378 (28.5)	371 (29.6)	3263 (28.0)	3053 (30.4)	588 (20.5)	
Eastern Europe, n (%)	2482 (30.7)	1285 (26.6)	290 (23.1)	3477 (29.9)	2832 (28.2)	934 (32.5)	
Asia Pacific, n (%)	1331 (16.5)	423 (8.7)	164 (13.1)	1586 (13.6)	1530 (15.3)	218 (7.6)	
Baseline health							
Baseline low-density lipoprotein cholesterol (mg/dL) (median, IQR)	75.48 (57.9, 97.3)	74.13 (55.2, 96.7)	76.06 (58.7, 97.7)	74.90 (56.8, 96.9)	74.90 (57.1, 97.3)	74.52 (56.8, 96.9)	0.67
Current smoker, n (%)	1565 (19.4)	888 (18.4)	252 (20.1)	2198 (18.9)	1755 (17.5)	690 (24.0)	<0.001
Hypertension, n (%)	5528 (68.3)	3956 (81.8)	975 (77.8)	8494 (72.9)	7270 (72.5)	2198 (76.5)	<0.001
Hyperlipidemia, n (%)	4907 (60.7)	3402 (70.3)	879 (70.1)	7417 (63.7)	6290 (62.7)	2008 (69.9)	<0.001
Diabetes mellitus (with or without pharmacotherapy, n (%))	2225 (27.5)	2231 (46.1)	491 (39.2)	3962 (34.0)	3303 (32.9)	1148 (40.0)	<0.001
Past myocardial infarction, n (%)	2386 (29.5)	1625 (33.6)	431 (34.4)	3578 (30.7)	3026 (30.2)	981 (34.1)	<0.001
Past percutaneous coronary intervention (PCI), n (%)	1791 (22.1)	1296 (26.8)	386 (30.8)	2698 (23.2)	2300 (22.9)	784 (27.3)	<0.001
ST-elevation myocardial infarction (STEMI), n (%)	3845 (47.5)	1992 (41.2)	529 (42.2)	5302 (45.5)	4540 (45.3)	1288 (44.8)	0.68
Non-STEMI, n (%)	3280 (40.6)	2244 (46.4)	559 (44.6)	4951 (42.5)	4240 (42.3)	1276 (44.4)	0.04
Unstable angina, n (%)	963 (11.9)	600 (12.4)	166 (13.2)	1395 (12.0)	1251 (12.5)	309 (10.8)	0.01
ST-segment deviation, n (%)	5922 (73.3)	3230 (66.8)	868 (69.3)	8272 (71.1)	7153 (71.3)	1985 (69.1)	0.02
Cath performed at OE, n (%)	6900 (85.3)	4208 (87.0)	1102 (87.9)	9987 (85.7)	8513 (84.9)	2577 (89.7)	<0.001

Continued

Table. Continued

Baseline Characteristic	Obstructive Sleep Apnea (OSA)		Short Sleep		Overnight shift work		P Value
	No OSA	OSA	<6 Hours	≥6 Hours	No	Yes	
PCI performed at QE, n (%)	6162 (76.2)	3738 (77.3)	981 (78.2)	8901 (76.4)	7580 (75.6)	2303 (80.2)	<0.001
Baseline estimated glomerular filtration rate <60 (mL/min), n (%)	866 (10.9)	621 (13.1)	161 (13.1)	1322 (11.6)	1170 (11.9)	314 (11.1)	0.23
Medications							
Aspirin, n (%)	7788 (96.3)	4677 (96.7)	1201 (95.8)	11 246 (96.6)	9660 (96.3)	2787 (97.0)	0.08
P2Y12 inhibitor, n (%)	7134 (88.2)	4279 (88.5)	1115 (89.0)	10 276 (88.2)	8808 (87.8)	2586 (90.0)	0.001
Statins, n (%)	7668 (94.8)	4555 (94.2)	1189 (94.9)	11 015 (94.6)	9482 (94.5)	2723 (94.8)	0.61
Beta blocker, n (%)	6998 (86.5)	4290 (88.7)	1078 (86.0)	10 193 (87.5)	8727 (87.0)	2545 (88.6)	0.03
ACE or ARB, n (%)	6588 (81.5)	4086 (84.4)	1065 (85.0)	9591 (82.3)	8251 (82.3)	2408 (83.8)	0.05
Protocol							
Days from qualifying event to randomization (median, IQR)	14.00 (6, 23)	15.00 (6, 23)	14.00 (5, 23)	14.00 (6, 23)	15.00 (6, 23)	14.00 (5, 22)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IQR, interquartile range.

on Berlin questionnaire¹⁹), and circadian rhythm disruption (≥1 year working at least 3 overnight shifts per week). Additional sensitivity analyses applied alternate sleep duration thresholds including <7 hours and >9 hours.²³ Kaplan–Meier event rates are reported at 3 years. Cox proportional hazards models were adjusted for age, sex, current smoker, race (white versus nonwhite), region, BMI, hypertension, hyperlipidemia, diabetes mellitus, past MI, past percutaneous coronary intervention, index diagnosis (ST-elevation myocardial infarction versus non-ST-elevation ACS), days from qualifying event, catheterization for qualifying event, baseline low-density lipoprotein cholesterol, Lp-PLA₂ activity, baseline estimated glomerular filtration rate <60 mL/min per 1.73 m², and randomized treatment arm. An integer risk score (0–3) was created based on the number of sleep-related risk factors that were present (OSA risk, sleep duration, and shift work). All tests were 2-sided with P<0.05 considered significant. All statistical computations were done with the SAS System (V9.3, 2010; SAS Institute Inc, Cary, NC).

Results

Overall, median age of the study population was 64 years and 74.5% were male. Patients with an elevated risk of OSA tended to be younger, white, and tended to have a higher BMI and a higher prevalence of hypertension and hyperlipidemia (Table). Patients with fewer hours of sleep tended to be younger, female, and nonwhite with higher BMI and more likely to have a history of hypertension and hyperlipidemia. Those individuals with more overnight shift work were more likely to be younger, male, and white, with higher BMI, and have a history of hypertension and hyperlipidemia (Table).

Mean reported sleep duration was 7.4 (±1.5) hours (median=7.5 hours), with 9.7% of patients reporting that they slept fewer than 6 hours daily. After multivariable adjustment, patients who reported sleeping fewer than 6 hours per night had a 29% higher risk of MCE (adjusted hazard ratio [adj HR], 1.29; 95% confidence interval [CI], 1.12–1.49; P=0.001) and a 15% higher risk of MACE (adj HR, 1.15; 95% CI, 0.98–1.35; P=0.08) than those who reported sleeping 6 hours or more per night (Figure 1). Risk of MI (adj HR, 1.13; 95% CI, 0.93–1.37; P=0.20) and all-cause mortality (adj HR, 1.03; 95% CI, 0.8, 1.32; P=0.83) were not significantly increased in patients who reported sleeping fewer than 6 hours per night. Sensitivity analyses comparing <7 hours of sleep to those with a normal sleep duration (7–9 hours) yielded qualitatively consistent results (MCE: adj HR, 1.18; 95% CI, 1.06–1.31; P=0.003; Table S1). Conversely, prolonged sleep duration >9 hours was associated with an increased risk of both all-cause mortality (adj HR, 1.38; 95% CI, 1.08–1.74) and cardiovascular death (adj HR, 1.41; 95% CI, 1.05–1.9), including directionally consistent results for MI and stroke (Table S2).

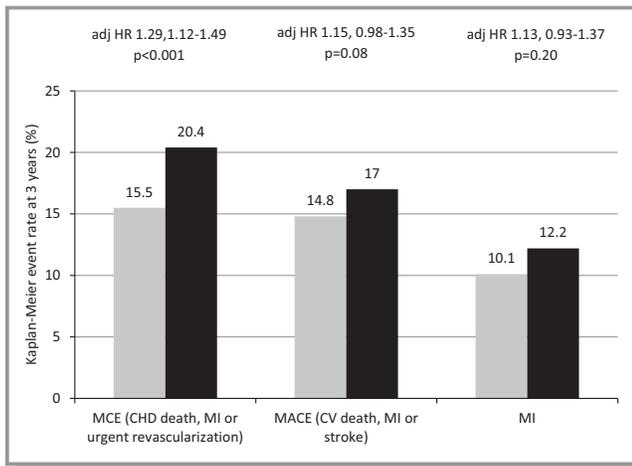


Figure 1. Adjusted risk of cardiovascular events based on reported sleep duration. Fewer than 6 hours of nightly sleep is indicated with a black bar and 6 hours or more with a gray bar. adj HR indicates adjusted hazard ratio; CHD, coronary heart disease; CV, cardiovascular; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction.

Of the 12 924 patients who completed the Berlin questionnaire, 37.4% (4840) screened positive for OSA. Within this group, by medical history, only 862 patients were reported to have a confirmed diagnosis of OSA at baseline and of whom 344 patients were described to be using noninvasive ventilation for OSA. After multivariable adjustment, patients at increased risk of OSA had a 12% higher risk of MCE (adj HR, 1.12; 95% CI, 1.00–1.24; $P=0.04$) and 13%

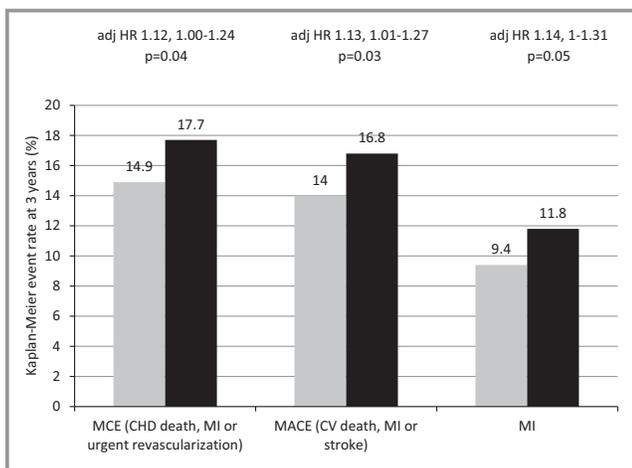


Figure 2. Adjusted risk of cardiovascular events based on risk of obstructive sleep apnea (OSA) as assessed by the Berlin questionnaire. Low risk of OSA is indicated by a gray bar and high risk of OSA with a black bar. adj HR indicates adjusted hazard ratio; CHD, coronary heart disease; CV, cardiovascular; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction.

higher risk of MACE (adj HR, 1.13; 95% CI, 1.01–1.27; $P=0.03$). Patients who screened positive for OSA had a borderline 14% higher risk of MI (adj HR, 1.14; 95% CI, 1.00–1.31; $P=0.05$) than patients who did not screen positive for OSA (Figure 2). All-cause mortality (adj HR, 0.99; 95% CI, 0.84–1.17; $P=0.89$) was not significantly increased in patients who screened positive for OSA.

At least 1 previous year of overnight shift work (≥ 3 overnight shifts per week) was reported in 22.3% of the patients. Of those patients, 44.0% had worked overnight shifts for 1 to 5 years, 21.1% for 6 to 10 years, and 34.8% for more than 10 years. After multivariable adjustment, those patients who reported working overnight shifts for at least 1 year had a 15% increased risk of MCE (adj HR, 1.15; 95% CI, 1.03–1.29; $P=0.01$), a 12% increased risk of MACE (adj HR, 1.12; 95% CI, 1.00–1.27; $P=0.06$) and a 21% increased risk of MI (adj HR, 1.21; 95% CI, 1.04–1.39; $P=0.01$) than those who did not report working overnight shifts (Figure 3). All-cause mortality risk was not increased in patients reporting overnight shift work (adj HR, 1.07; 95% CI, 0.89–1.29; $P=0.44$).

An integer risk score was created for individuals who had ≥ 1 sleep-related risk factors (risk of OSA, short sleep duration, or circadian disruption associated with shift work). A step-wise increase in risk of MCE was observed for individuals with increasing sleep risk score, including >2 -fold higher risk of MCE for individuals with all 3 sleep-related risk factors (adj HR, 2.01; 95% CI, 1.49–2.71; $P<0.001$) versus those with none. Similarly, individuals with 3 sleep-related risk factors were at increased risk of MACE (adj HR, 1.66; 95% CI, 1.18–2.33; $P=0.004$), MI (adj HR, 1.81; 95% CI, 1.23–2.67; $P=0.003$), all-cause mortality (adj HR, 2.01; 95% CI, 1.22–

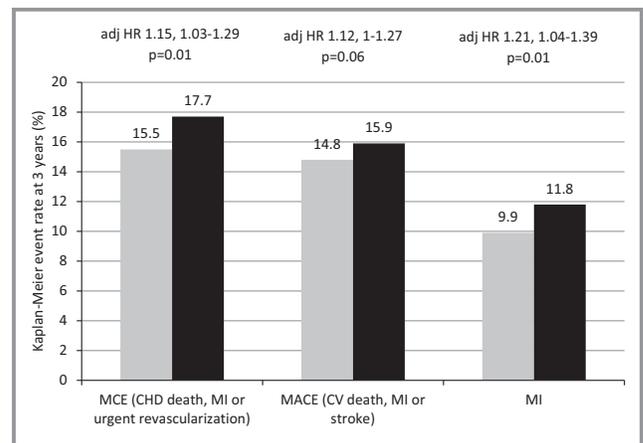


Figure 3. Adjusted risk of cardiovascular events based on history of overnight shift work. Patients with at least 1 year of overnight shift work (≥ 3 nights/week) are indicated with a black bar. adj HR indicates adjusted hazard ratio; CHD, coronary heart disease; CV, cardiovascular; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction.

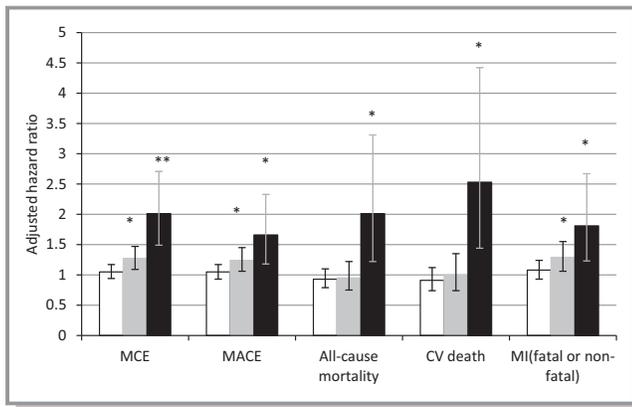


Figure 4. Adjusted risk of cardiovascular events based on the number of positive sleep-related factors (ie, risk of obstructive sleep apnea, short sleep duration, and history of shift work). No sleep-related factors is the referent group. One sleep-related risk factor is indicated by an open bar, 2 sleep-related risk factors is indicated by a gray bar, and 3 sleep-related risk factors is indicated by a black bar (* $P \leq 0.01$; ** $P \leq 0.001$). CV indicates cardiovascular; MACE, major adverse cardiac events; MCE, major coronary events; MI, myocardial infarction.

3.31; $P=0.006$), and cardiovascular death (adj HR, 2.53; 95% CI, 1.44–4.42; $P=0.001$; Figure 4).

Discussion

In our global, prospective study of over 13 000 patients who recently suffered an ACS, we found that OSA, short sleep duration, and overnight shift work were each independently associated with increased risk of MCE. Furthermore, the presence of multiple sleep-related risk factors led to an additive increase in cardiovascular risk. With cardiovascular disease being the leading cause of death worldwide overall²⁴ and in those in the United States aged 65 years and older,²⁵ our results indicate that short sleep duration, OSA, and recurrent circadian disruption induced by overnight shift work may be detrimental to cardiovascular health outcomes in this older population of post-ACS patients independent of traditional risk factors.

Sleep Duration

Almost 10% of this post-ACS patient cohort reported an inadequate duration of sleep with fewer than 6 hours per night, on average, and those individuals were found to be at increased risk of MCE and MACE. Prevalence of inadequate sleep duration in the current study is comparable to adults in the general population who in the Multinational Time Use Survey reported sleeping 6 hours or fewer in Norway (6%), Italy (7%), Switzerland (7%), Sweden (5%), United Kingdom (10%), and United States 9 (%).²⁶ Epidemiological data have

demonstrated that sleep deficiency is associated with important negative health consequences, including increased incidence of obesity, diabetes mellitus, hypertension, and cardiovascular events.^{27–32} To that end, in the Sleep Heart Health Study, risk of hypertension was higher in those sleeping <6 hours (odds ratio, 1.66) per night compared with 7- to 8-hours sleepers.²⁹ Moreover, in hypertensive patients, short sleep duration (<7.5 hours per night) is predictive of incident stroke or MI (HR, 1.68).³¹ In the general population, short sleep duration has also been shown to be associated with the presence of coronary artery calcification.⁶ Additionally, among the general population, all-cause mortality has been shown to be higher in short-duration (≤ 5 hours per night) and prolonged-duration sleepers (>9 hours) as compared with those with more normal sleep duration.^{33,34} Our data suggest that the association between short sleep duration and adverse cardiovascular events in the general population holds true for post-ACS patients. Similarly, prolonged sleep duration was associated with an increased risk of both all-cause mortality and cardiovascular mortality. In both instances, it remains unknown whether other comorbid conditions that contribute to either shortened or prolonged sleep may contribute to the observed findings, although the relationship remained significant after adjustment for known confounders.

Obstructive Sleep Apnea

We have found that more than 1 in 3 adults in this study screened positive for OSA. This prevalence is generally consistent with the reported OSA prevalence in the United States of ≈ 1 in 3 adult men and 1 in 6 adult women.¹⁰ Risk of OSA has substantially increased over the past 2 decades and increases with increasing age.¹⁰ Surveys of ≈ 5000 police officers³⁵ and nearly 7000 firefighters³⁶ revealed that more than 80% of those identified at risk of OSA were undiagnosed and untreated. Even in this population of ACS patients, who likely have more extensive contact with physicians, 82% of those who screened positive were undiagnosed and 93% were untreated. Heart failure patients with OSA have a higher readmission rates than heart failure patients without OSA.³⁷ In the general population, the observed relationship between OSA and recurrent cardiovascular events in this post-ACS population is consistent with previously reported associations in the general population between OSA and incident cardiovascular health outcomes.^{4,11–13}

Overnight Shift Work

More than 20% of the ACS patient population reported working overnight shifts for at least 1 year in their lifetime. This is consistent with the $\approx 15\%$ of full-time workers in the

United States who are shift workers; an estimated 8 million of these shift workers regularly working during the overnight hours.³⁸ Japan, Australia, the United Kingdom, and France report similar rates of shift work.³⁹ The current post-ACS population with a history of overnight shift work was found to be at increased risk of MCE, MACE, and MI. Overnight shift work disrupts the alignment of the endogenous circadian clock, responsible for the 24-hour rhythm of alertness, physiology, and behavior, and is associated with daytime sleep that is shorter and less consolidated.⁴⁰ Past studies have suggested that overnight shift work is associated with a 40% increase in the risk of cardiovascular disease,⁴¹ as well as a higher prevalence of atherosclerosis,⁴² and increased triglycerides.⁴³ Night shift work within the past 5 years was associated with an increased risk of MI.⁴⁴ The increased risk of adverse cardiovascular outcomes in post-ACS shift workers is consistent with these adverse outcomes in shift workers in general.

Combination of Sleep-Related Factors

Notably, we found that the presence of multiple sleep-related risk factors has an additive effect in regards to cardiovascular risk. To our knowledge, this is the first study to evaluate the cumulative impact of short sleep duration, OSA risk, and shift work history on cardiovascular outcomes. Further investigation of these inter-related factors is important because these sleep-related factors are often interconnected. For instance, those who work overnight shifts often have reduced sleep duration and quality during the daytime hours,⁴⁰ and the frequent awakenings in individuals with OSA may result in overall shorter duration of sleep. Thus, it is important to evaluate the combined effect of these sleep-related factors. It should be noted that the ACS-patient population in this study is already at very high risk for adverse cardiovascular outcomes as compared with the general population. Given the high likelihood of another cardiovascular event and the associations we reveal in this study, we believe there is a critical need to evaluate sleep-related interventions in the post-ACS population.

Mitigating Risk

Empirically supported sleep health interventions may include education on the importance of obtaining sleep of adequate quantity and quality as a critical first step in improving sleep health.^{23,45} Easily administered screening tools, such as the 10-item Berlin questionnaire that we used, together with simplified diagnostic methods such as home sleep testing for OSA,⁴⁶ are becoming increasingly available and may be appropriate for screening in post-ACS patients. Interventions and education to treat sleep disorders, especially OSA, and to

increase sleep duration⁴⁷ may prove to be effective in reducing adverse cardiac events. Although a recent report that 3.3 hours of nightly continuous positive airway pressure did not prevent cardiovascular events in patients with moderate-to-severe sleep apnea,⁴⁸ the identification, diagnosis, and treatment of OSA should be further investigated. A previous trial has shown that sleep was improved in ACS patients by treating depressive symptoms.⁴⁹ Because of demands for business to be conducted around the clock, the need for overnight shift work will continue. Therefore, mitigations must be made to stabilize sleep timing in order to minimize circadian disruption and thereby improve daytime sleep. These interventions should be evaluated in the vulnerable post-ACS patient population.

Limitations

The study design was limited to a self-reported questionnaire, and there was a lack of objective confirmation of these reported sleep-related factors. We did not assess how recently the overnight shift work was performed and whether the frequency of shift work changed after their ACS. Further research is required to determine whether more-recent shiftwork confers greater risk in the post-ACS patient. Although patients were followed for a median of more than 2 years, it is possible that additional cardiovascular risk would be more apparent with time. Although we adjusted for multiple variables, we cannot exclude the possibility of residual confounding and therefore causality cannot be definitively demonstrated. We also acknowledge that physiological or behavioral mechanisms that are indirectly related to sleep disorders may contribute to the elevated risk of cardiovascular outcomes. These additional mechanisms may include intermittent hypoxia in OSA, behavior, and lifestyle factors in short sleepers and shift workers and impaired metabolism in shift work. Further research should explore the potential physiological link between sleep duration, sleep disruption, sleep disorders, and cardiovascular risk.

The Berlin questionnaire has not been validated in a population of post-ACS patients, but has been validated in small studies of cardiovascular or cerebrovascular disease patients.²² There could potentially be increased central sleep apnea in heart failure patients or increased sleepiness attributed to medical conditions, which might affect the estimate on risk on this screening questionnaire. Furthermore, sleep habits may or may not have changed post-ACS.

Conclusion

In patients post-ACS, insufficient sleep, whether caused by reduced sleep duration, OSA, or recurrent circadian disruption induced by overnight shift work, is associated with an

increased risk of recurrent cardiovascular events. These sleep-related factors are not routinely assessed and, as such, are under-recognized as important predictors of adverse outcomes post-ACS. Increased efforts should be made to educate patients and their healthcare providers about the importance of sleep and sleep health. Given the elevated risk of patients post-ACS, considerations should be made to screen all post-ACS patients for sleep disorders and insufficient sleep in order to implement appropriate interventions and patient education.⁴⁵

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Supplemental Material

Table S1. Adjusted risk of CV events based on reported sleep duration of <7 hours as compared to reported sleep duration of ≤ 7 hours and ≤ 9 hours

Event	Sleep duration of <7 hours	Sleep duration of ≥ 7 and ≤ 9 hours	Unadjusted Model		Adjusted Model	
	Kaplan-Meier event rate at 3 years (%)	Kaplan-Meier event rate at 3 years (%)	HR(95% CI)	P value	HR(95% CI)	P value
MCE	591 (17.92)	1054 (14.82)	1.24 (1.12, 1.37)	<.0001	1.18 (1.06, 1.31)	0.003
MACE	515 (16.12)	977 (14.11)	1.15 (1.04, 1.28)	0.009	1.12 (1, 1.25)	0.05
All-cause mortality	212 (6.46)	451 (6.94)	1.02 (0.86, 1.2)	0.84	1.07 (0.9, 1.26)	0.47
CV death	149 (4.73)	293 (4.26)	1.1 (0.91, 1.35)	0.32	1.15 (0.94, 1.42)	0.18
MI	357 (11.42)	651 (9.7)	1.2 (1.05, 1.36)	0.006	1.12 (0.98, 1.28)	0.11
Stroke	82 (2.71)	164 (2.4)	1.09 (0.83, 1.42)	0.54	1.08 (0.82, 1.43)	0.58

Age, sex, current smoker, race(white vs non-white), region, BMI, hypertension, hyperlipidemia, diabetes mellitus, prior MI, prior PCI, index diagnosis(STEMI vs non-STE ACS), days from qualifying event, catheterization for qualifying event, baseline LDL cholesterol, LpPLA2, baseline eGFR<60 and randomized treatment arm were adjusted in the model.

Table S2. Adjusted risk of CV events based on reported sleep duration of >9 hours.

Event	Sleep duration of >9hours	Sleep duration of ≥7 and ≤9 hours	Unadjusted Model		Adjusted Model	
	Kaplan-Meier event rate at 3 years (%)	Kaplan-Meier event rate at 3 years (%)	HR(95% CI)	P value	HR(95% CI)	P value
Major coronary events (MCE),	154 (18.03)	1054 (14.82)	1.25 (1.06, 1.48)	0.009	1.11 (0.93, 1.33)	0.24
Major adverse cardiac events (MACE)	156 (18.12)	977 (14.11)	1.37 (1.16, 1.63)	0.0002	1.17 (0.98, 1.4)	0.08
All-cause mortality	93 (11.57)	451 (6.94)	1.74 (1.39, 2.18)	<.0001	1.38 (1.08, 1.74)	0.009
Cardiovascular death (CV)	62 (7.2)	293 (4.26)	1.79 (1.36, 2.35)	<.0001	1.41 (1.05, 1.9)	0.02
Myocardial infarction (MI)	96 (10.98)	651 (9.7)	1.26 (1.02, 1.57)	0.032	1.1 (0.88, 1.39)	0.40
Stroke	26 (3.41)	164 (2.4)	1.34 (0.89, 2.03)	0.16	1.14 (0.73, 1.77)	0.56

Age, sex, current smoker, race(white vs non-white), region, body mass index, hypertension, hyperlipidemia, diabetes mellitus, prior MI, prior percutaneous coronary intervention (PCI), index diagnosis(ST-Elevation Myocardial Infarction (STEMI) vs non-STE ACS), days from qualifying event, catheterization for qualifying event, baseline low-density lipoprotein (LDL) cholesterol, lipoprotein-associated phospholipase-A2 (LpPLA2), baseline estimated glomerular filtration rate (eGFR)<60 and randomized treatment arm were adjusted in the model.

Figure S1. Sleep Questionnaire for the SOLID-TIMI 52 Trial



Sleep Questionnaire for the SOLID-TIMI 52 Trial

Instructions: You should complete the questionnaire yourself. If you have difficulty completing the questionnaire by yourself, other people can help (for example, a family member, friend or your study coordinator) by reading the questions to you and marking your answers for you.

1. **Have you been told that you snore?**

- YES
- NO
- DON'T KNOW

If you answered NO or DON'T KNOW to question 1, skip to question 5.

(Note: Answer 2, 3, and 4 only if you answered YES to 1)

2. If you snore, your snoring is:

- slightly louder than breathing
- as loud as talking
- louder than talking
- very loud, can be heard in adjacent rooms

3. How often do you snore?

- nearly every day
- 3-4 times a week
- 1-2 times a week
- 1-2 times a month
- never or nearly never

4. Has your snoring ever bothered other people?

- Yes
- No

5. Has anyone told you that you quit breathing during your sleep?

- nearly every day
- 3-4 times a week
- 1-2 times a week
- 1-2 times a month
- never or nearly never

6. I feel tired or fatigued after sleep...

- nearly every day
- 3-4 times a week
- 1-2 times a week
- 1-2 times a month
- never or nearly never

7. During my waking hours, I feel tired, fatigued or not up to par...

- nearly every day
- 3-4 times a week
- 1-2 times a week
- 1-2 times a month
- never or nearly never

8a. I have nodded off or fallen asleep while driving a vehicle...

- Yes
- No

b. If YES, how often does this occur?

- nearly every day

- 3-4 times a week
- 1-2 times a week
- 1-2 times a month
- never or nearly never

9. How many years have you worked at least ONE overnight shift per week?

_____ years

N/A

(Overnight work is defined as at least 6 hours on duty between 10 PM and 8 AM)

10. How many years have you worked at least THREE overnight shifts per week?

_____ years

N/A

(Overnight work is defined as at least 6 hours on duty between 10 PM and 8 AM)

11. On average, how much sleep do you get in 24 hours:

_____ hours _____ minutes